



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/727,779

12/03/2003

Shea N. Gardner

IL-11191

7079

24981

7590

07/20/2010

Lawrence Livermore National Security, LLC
LAWRENCE LIVERMORE NATIONAL LABORATORY
PO BOX 808, L-703
LIVERMORE, CA 94551-0808

EXAMINER

BERTAGNA, ANGELA MARIE

ART UNIT

PAPER NUMBER

1637

MAIL DATE

DELIVERY MODE

07/20/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SHEA N. GARDNER,
RAYMOND P. MARIELLA JR., ALLEN T. CHRISTIAN,
JENNIFER A. YOUNG, and DAVID S. CLAGUE

Appeal 2009-011563
Application 10/727,779
Technology Center 1600

Before ERIC GRIMES, DONALD E. ADAMS, and LORA M. GREEN,
Administrative Patent Judges.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL¹

This is an appeal under 35 U.S.C. § 134 involving claims to a method of synthesizing a DNA molecule. The Examiner has rejected the claims as anticipated, obvious, and including new matter. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

¹ The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the “MAIL DATE” (paper delivery mode) or the “NOTIFICATION DATE” (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF THE CASE

Claims 11, 16, and 17 are on appeal and read as follows:

11. A method of producing a DNA molecule of 1-10 kilobases of user-defined sequence from short oligos of length n (n -mers), comprising the steps of:

- virtually preselecting a multiplicity of DNA sequence segments that will comprise said DNA molecule of user-defined sequence by using computational techniques to virtually break said user-defined sequence into virtual fragments of length n (n -mers) of defined size,

- providing fragments in vitro by providing fragments of length n (n -mers) of defined size that correspond to said virtual fragments,

- arraying fragments in vitro by arraying said fragments of length n (n -mers) of defined size into groups,

- separating DNA sequence segments temporally in vitro by separating said DNA sequence segments of length n (n -mers) of defined size temporally, and

- assembling groups in vitro by assembling said groups into double-strand DNA molecules of predetermined base-pairs using parallel synthesis, DNA shuffling, and DNA polymerase wherein said step of separating said DNA sequence segments temporally and said step of assembling said groups into double-strand DNA molecules of predetermined base-pairs is accomplished by said DNA sequence segments being added gradually, in an order that is predicted computationally to minimize errors to produce said DNA molecule of user-defined sequence, and

- wherein said step or [sic] assembling said groups into double-strand DNA molecules utilizes starting oligos of length n (n -mers) where n is an odd number.

16. The method of producing a DNA molecule of user-defined sequence of claim 11 wherein said starting oligos of length n (n -mers) where n is an odd number are starting oligos of length $n+1$ or $n+2$.

17. The method of producing a DNA molecule of 1-10 kilobases of user-defined sequence from short oligos of length n (n -mers) of claim 11 wherein said multiplicity of DNA sequence segments comprise oligos in multiple reading frames.

The claims stand rejected as follows:

- Claim 16 under 35 U.S.C. § 112, first paragraph, on the basis that it includes new matter (Ans. 4);
- Claim 11 under 35 U.S.C. § 102(e) as anticipated by Evans² (Ans. 5);
- Claims 16 and 17 under 35 U.S.C. §§ 102(a) and 102(e) as anticipated by Evans (Ans. 7);
- Claims 11 and 17 under 35 U.S.C. § 103(a) as obvious in view of Selifonov³ and Evans (Ans. 8); and
- Claim 16 under 35 U.S.C. § 103(a) as obvious in view of Selifonov, Evans, and Murphy⁴ (Ans. 11).

I.

The Examiner has rejected claim 16 on the basis that the limitation that the “starting oligos [are] of length $n+1$ or $n+2$ ” is new matter (Ans. 4-5). The Examiner finds that the Specification “teaches in paragraphs 63 and 64 that the starting oligos have a length of $n+1$, $n+2$, *etc*, but does not provide support for a broader embodiment of the method wherein starting oligos having a length of $n+1$ or $n+2$. . . are used” (Ans. 5).

Appellants contend that the Specification describes starting oligos having length $n+1$ and starting oligos having length $n+2$, and therefore

² Evans, US Patent Application Publication No. 2003/0087238 A1, published May 8, 2003

³ Selifonov et al., WO 00/42560, published July 20, 2000

⁴ Murphy et al., US Patent 6,994,963 B1, issued Feb. 7, 2006

provides support for the claim limitation of starting oligos having length $n+1$ or $n+2$ (Appeal Br. 14-15).

We agree with Appellants that the Examiner has not shown that the disputed limitations lacks adequate support in the Specification. The Examiner has acknowledged that the Specification discloses starting oligos with length $n+1$, as well as starting oligos with length $n+2$ (Ans. 5). It is true that paragraphs 63 and 64 of the Specification contemplate the $n+1$ and $n+2$ oligos being used together in a mixture of different-sized oligos, but the Examiner has not disputed that the Specification also discloses carrying out the method of claim 11 with oligos that are all the same size. Whether the length of the oligos is considered to be “ n ” or “ $n+1$ ” or “ $n+2$ ” nucleotides is a matter of semantics; a person of ordinary skill in the art would recognize a description of the disputed limitation in the Specification.

II.

Issue

The Examiner has rejected claim 11 under 35 U.S.C. § 102(e), and claims 16 and 17 under 35 U.S.C. §§ 102(a) and 102(e), as anticipated by Evans (Ans. 5, 7). The Examiner finds that Evans discloses all of the limitations of claim 11, and points to specific passages to support her findings (*id.* at 5-7). The Examiner also finds that Evans discloses the “ $n+1$ or $n+2$ ” limitation of claim 16 and the “multiple reading frames” limitation of claim 17 (Ans. 7).

Appellants contend that Evans does not disclose some of the elements of claim 11 (Appeal Br. 17) or the precise combination of elements recited in claim 11 (*id.* at 18). More specifically, Appellants contend that Evans does not disclose assembling DNA molecules using DNA shuffling (Reply

Br. 5) or adding segments in an order computationally predicted to minimize errors (*id.*), or using starting oligos having an odd number of nucleotides (*id.* at 6). Appellants also contend that Evans does not disclose the additional limitations of claims 16 and 17 (Appeal Br. 19-22, Reply Br. 8-9).

The issue with respect to the anticipation rejections is: Does the evidence of record support the Examiner's findings that Evans discloses a process that includes all the limitations of each of claims 11, 16, and 17?

Findings of Fact

We adopt the Examiner's findings of fact (Office Action mailed Sept. 26, 2008, pages 5-6; Ans. 5-7) with the exception of her finding that Evans discloses using oligos in multiple reading frames. The additional facts below are supported by a preponderance of the evidence:

1. The Specification states that the "assembly process is substantially the same as the process called DNA shuffling. It is similar to PCR in that there is a template, a primer, a DNA polymerase, and the attendant nucleotides and buffers. It is dissimilar to PCR in that the primer and template are the same entities – the n-mers themselves." (Spec. 20, ¶ 48.)

2. The Specification states that "oligos are added gradually, in sequence order or other order that is predicted (computationally) to minimize errors, over time through the many thermocycles of hybridization and polymerization" (*id.* at 23, ¶ 53).

3. The Specification states that "Applicants add the oligos gradually, over multiple thermocycles, to each well, thus further reducing the likelihood that an oligo at one end of the sequence will bind to one that is distant in the desired sequence (i.e., out of order)" (*id.* at 24, ¶ 56).

4. The Specification states that using “oligos from overlapping multiple reading frames within the same PCR reaction” (*id.* at 24, ¶ 57) involves “the same sequence of DNA [being] spanned by multiple oligos of length n, each frame-shifted from one another, and combined in the same well (i.e. the same PCR reaction). Thus, a given sequence would be represented more than once by oligos in different reading frames that will hybridize with different overlap lengths.” (*Id.* at 25, ¶ 58.)

Analysis

We agree with the Examiner that Evans discloses all of the limitations of claims 1 and 16 at the places identified by the Examiner. Appellants’ contrary contentions (Appeal Br. 17-22) are unpersuasive because Appellants do not provide any fact-based reasoning in support of their contention that the Examiner’s findings are in error.

As to Appellants’ more specific contentions that Evans does not disclose DNA shuffling, adding segments in a computationally predicted order, and starting oligos of an odd number of nucleotides (Reply Brief 5-6), the Examiner pointed to passages of Evans disclosing these limitations and we agree with her findings. The Specification defines “DNA shuffling” to mean a PCR process in which the primers also serve as templates (FF 1). That limitation is disclosed by Evans (Evans, ¶¶ 93-94, Fig. 16).

The Specification states that adding DNA segments in an order computationally predicted to minimize error simply requires adding them gradually, in sequence order (FF 2). Sequential addition of oligos is disclosed by Evans (Evans, ¶ 58). Evans also discloses that the starting oligos can be an odd number of nucleotides in length (*id.* at ¶ 82) and that

they can be of length n , $n+1$, or $n+2$ nucleotides (*id.* at ¶ 53: “15, 16, [or] 17 . . . bases”).

With regard to claim 17, Appellants argue that Evans does not disclose using oligos in multiple reading frames (Reply Br. 8-9). The Examiner reasons that “Evans teaches variation of the oligo length and overlap between the fragments (paragraphs 53 and 54). These DNA fragments inherently comprise multiple reading frames.” (Ans. 7.)

The Specification, however, defines “reading frames” in the context of the claimed method to have a meaning different from its usual art-accepted meaning. The Specification states that, when oligos from multiple reading frames are used in a PCR reaction, “a given sequence [is] represented more than once by oligos . . . that will hybridize with different overlap lengths” (Spec. 25, ¶ 58). Thus, in order for Evans to anticipate claim 17, it must disclose carrying out its primer extension reaction using multiple oligos that hybridize to a given target sequence with different degrees of overlap. The Examiner has not pointed to any disclosure of this limitation in Evans and therefore has not made out a *prima facie* case that Evans anticipates claim 17.

Conclusion of Law

The evidence of record supports the Examiner’s findings that Evans discloses a process that includes all the limitations of each of claims 11 and 16, but does not support her finding that Evans discloses a process that includes all the limitations of claim 17.

III.

Issue

The Examiner has rejected claims 11 and 17 as obvious in view of Selifonov and Evans (Ans. 8) and claim 16 as obvious in view of Selifonov, Evans, and Murphy. We affirm the rejection of claim 11 based on Selifonov and Evans and the rejection of claim 16 based on Selifonov, Evans, and Murphy because these claims are anticipated by Evans. Anticipation is the epitome of obviousness. *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002).

With regard to claim 17, the Examiner finds that “Selifonov teaches variation of the oligo length and overlap between the fragments (page 33, lines 1-6). These DNA fragments inherently comprise multiple reading frames.” (Ans. 9-10.)

Appellants contend that Selifonov and Evans do not disclose using oligos in multiple reading frames (Appeal Br. 25; Reply Br. 12-13).

We agree with Appellants that the Examiner has not shown that the cited references teach or would have made obvious using oligos in multiple reading frames, when that claim language is interpreted in light of the Specification. As discussed above, the Specification states that “multiple reading frames” means that, in a given PCR reaction, “a given sequence [is] represented more than once by oligos . . . that will hybridize with different overlap lengths” (FF 4). The Examiner’s reasoning – that oligos with variable length and overlap will inherently comprise multiple reading frames – does not adequately explain why it would have been obvious to practice Evans’ method using multiple oligos that hybridize to the same target sequence with different amounts of overlap, as required by claim 17

Appeal 2009-011563
Application 10/727,779

when “multiple reading frames” is read in light of the Specification. The Examiner therefore has not made out a prima facie case that claim 17 would have been obvious based on Selifonov and Evans.

SUMMARY

We affirm the rejection of claims 11 and 16 under 35 U.S.C. §§ 102 and 103. We reverse the rejection of claim 16 under 35 U.S.C. § 112, first paragraph, and the rejection of claim 17 under 35 U.S.C. §§ 102 and 103.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

lp

LAWRENCE LIVERMORE NATIONAL SECURITY, LLC
LAWRENCE LIVERMORE NATIONAL LABORATORY
PO BOX 808, L-703
LIVERMORE CA 94551-0808